REMARKS

I Comments regarding restriction requirement

Claims 29, 32, 34, 43 and 44 are "method of use" claims which all depend from the independent product claims 10. Therefore, upon allowance of product claims 10, the method of use claims 29, 32, 34, 43 and 44 should be rejoined and considered together, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

II Indefinite rejection under 35 U.S.C. §112, second paragraph

Claims 35 and 38 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. Specifically, the Examiner has contended that "[t]he term 'specificity' recited in claims 35 and 38 is ambiguous and unclear and the metes and bounds of the claimed specificity is not defined." (12/03/03 Office Action, at page 2).

Applicants traverse this rejection, The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph in that claims 35 and 38 define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. Further, the courts have applied this standard to the antibody arts. See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph because: i) Applicants submit that the term specificity was well understood by those skilled in the antibody arts at the time of the filing of the invention; and ii) Applicants have included scientific references in the specification explaining specificity, including references for assays to measure antibody specificity. (See the Specification, for example, at page 23, lines 26-34, and page 24, lines 9-36. Thus, claims 35 and 38, when read in light of the specification, reasonably apprise those skilled in the art of the scope of the invention and give fair notice of what constitutes infringement of those claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

III Utility rejection under 35 U.S.C. §101

Claims 10, 30, 31, 33, 35-42 and 45-46 stand rejected under 35 U.S.C. § § 101 and § 112, first paragraph based on the allegation that the claimed invention lacks patentable utility. Specifically, the Examiner asserts that " the claimed invention is not supported by either a specific or substantial utility or a well established utility." (12/03/03 Office Action at page 2) Applicants traverse this rejection as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

Embodiments of Applicants' invention are directed to antibodies which specifically bind to polypeptides related to a human cell junction PDZ protein (CJPDZ). As described in the Specification at page 12, lines 10-23:

> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Figures 1A, 1B, and 1C. CJPDZ is 233 amino acids in length and has five potential protein kinase C phosphorylation sites at S52, T89, S181, T189, and T205. CJPDZ has chemical and structural similarity with C. elegans LIN-7 (GI 1685067; SEQ ID NO:3). CJPDZ and LIN-7 share 53% identity overall and 69% identity within the region from L25 to R204 of CJPDZ and from L117 to R295 of LIN-7, as shown in Figure 2. Within this region, CJPDZ contains a putative PDZ domain from R107 to T189 which shares 82% sequence identity with the PDZ domain of LIN-7. The GD dipeptide and asparagine residue found in nearly all PDZ domains are conserved in CJPDZ at G152, D153, and N159. In addition, the putative PDZ domain of CJPDZ contains eleven glycine residues, consistent with the glycine-rich nature of nearly all PDZ domains. A fragment of SEQ ID NO:2 from about nucleotide 432 to about nucleotide 461 is useful in hybridization or amplification technologies to identify SEQ ID NO:2 and to distinguish between SEQ ID NO:2

and a related sequence. Northern analysis shows the expression of this sequence in mononuclear cells derived from umbilical cord blood, in the testis, in fetal lung, and in breast tissue.

These antibodies have a variety of utilities, in particular in expression profiling, and for diagnosis of conditions or diseases characterized by expression of CJPDZ, for toxicology testing, and for drug discovery (see the Specification, for example, at page 29, lines 20-27; and page 33, line 36 to page 37, line 10).

In further support of the utility of the invention, Applicants submit with this response two expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before or shortly after the September 11, 1998 priority date of the instant application. The Rockett Declaration and the Iyer Declaration, and the ten (10) references establish that, prior to the filing dates of the provisional applications to which the subject application is benefitted priority, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;
>
> biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Office Action does not dispute that the polynucleotides described in the subject application can be used as a probe in cDNA microarrays and used in gene expression monitoring applications and likewise, the use of antibodies which specifically bind to the polypeptides encoded by these polynucleotides in such applications. Instead, the Patent Examiner contends that these polynucleotides cannot be useful without precise knowledge of their biological function, or the biological function of the polypeptides they encode. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Rockett Declaration and the Iyer Declaration the person of ordinary skill in the art can achieve beneficial results from these polynucleotides in the absence of any knowledge as to the precise function of the proteind encoded by them. The uses

of the claimed antibodies in gene expression monitoring applications are in fact independent of the precise biological function of biological functions of the proteins to which the antibodies specifically bind..

IV Enablement rejection under 35 U.S.C. §112, first paragraph

Claims 10, 30, 31, 33, 35-42 and 45-46 have been rejected for allegedly failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph. The Examiner has asserted that claims 10, 30, 31, 33, 35-42 and 45-46 are not patentable under the first paragraph of 35 U.S.C. §112 "because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility" (12/03/03 Office Action at page 2) and because the specification allegedly does not provide enablement commensurate in scope with the claims. (See Id.)

To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it should be withdrawn.

In regard to the remainder of the rejection, the Examiner has asserted that claims 10, 30, 31, 33, 35-42 and 45-46 are not patentable under the first paragraph of 35 U.S.C. §112 because the Specification allegedly does not provide enablement commensurate in scope with the claims. Applicants respectfully traverse this rejection for the following reasons.

The instant Office Action does not dispute that an enabling disclosure has been provided for antibodies which specifically bind to polypeptides comprising the amino acid sequence of SEQ ID NO:1. Rather, the Action alleges that an enabling disclosure has not been provided for antibodies which specifically bind to the recited "variants" of SEQ ID NO:1.

At the outset, the use of the antibodies which specifically bind the recited "variants" of SEQ ID NO:1 should not be at issue. That is, these antibodies have the same uses as an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

For example, the skilled artisan could use the claimed antibodies to purify a protein having an amino acid sequence comprising a variant sequence of SEQ ID NO:1 (See the Specification, for example, at page 41, lines 24-34). In another use, antibodies to variants of the amino acid sequence of SEQ ID NO: 1 can be used for drug screening purposes (See the Specification, for example, at page 33 line 36 to page 34 line 14). Additionally, antibodies which specifically bind to variants of SEQ ID NO:1 can be used, for example, in 2D-PAGE analysis for expression profiling related to toxicology testing, drug discovery and disease diagnosis. Thus, Applicants submit that the skilled artisan would readily know how to use antibodies to a "variant" of the sequence of SEQ ID NO: 1 and that undue experimentation would not be required.

Moreover, there should be no issue with how to make the antibodies *per se*. Methods for making antibodies are well known in the art, and are also described in the Specification at, for example, pages 22-24. The same methods for producing antibodies to polypeptides which comprise SEQ ID NO:1 could be used to make antibodies which specifically bind "variants" of SEQ ID NO:1.

Thus, the rejection appears to based on the presumption that one could not make the claimed antibodies because one would allegedly not be able to make the recited "variants" of SEQ ID NO:1 *per se*, which in turn are used to produce antibodies which specifically bind those proteins. Such, however, is not the case.

Note that claim 10 recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of CJPDZ) and SEQ ID NO:2 (the polynucleotide sequence encoding CJPDZ), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature. (Specification at page 10, lines 28-32)

For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art. (Specification at page 13, lines 25 to page 14, line 8)

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding CJPDZ or closely related molecules may be used to identify nucleic acid sequences which encode CJPDZ. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding CJPDZ, allelic variants, or related sequences.

> Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the CJPDZ encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the CJPDZ gene. (Specification at page 30, lines 6-16)
>
> See also Example VI at page 38.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Conventional methods for making antibodies, such as those described at pages 22-24 of the Specification, could the be used to make antibodies which specifically bind to the recited polypeptide variants.

The Examiner cited Coleman *et al.*, Abaza *et al.*, Lederman *et al.*, and Li *et al.*, as demonstrating that even a single amino acid change can alter protein function. However, these references are not relevant to the case at hand. In these cases, the mutations were "artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by these references would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of these references are not relevant to the case at hand, which relates to naturally occurring amino acid sequences.

The Examiner further cites Ngo *et al.* and alleges that due to the fact that the relationships between the sequence of a protein/peptide and its tertiary structure (i.e., its activity) are not well understood and are not predictable, it would require an undue experimentation for one skilled in the art to arrive at polypeptides comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1. However, the document cited by the Examiner relating to structure-antigenicity relationships in proteins is simply not germane to whether one can make and use the polypeptide variants recited by the present claims. That is, regardless of the precise functional characteristics of the SEQ ID NO:1 variants, one can still make those polypeptide variants using the disclosure provided by the present Specification. The polypeptides could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc.

Furthermore, the Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 10 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as CJPDZ-like proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential CJPDZ-like proteins related to SEQ ID NO:1, i.e., those CJPDZ-like proteins having as little as 30% identity over at least 150

residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a CJPDZ-like protein.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement***. [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies which specifically bind to the recited "variants" and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited "variants" and fragments of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection is requested.

V Written description rejection under 35 U.S.C. §112, first paragraph

Claims 10, 30, 31, 33, 35-42 and 46 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This rejection is improper,

as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991)

The Examiner's Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" of SEQ ID NO:1.

The subject matter encompassed by claims 10, 30, 31, 33, 35-42 and 46 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 10 recites a "naturally-occurring polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the specification. (See, for example, the Sequence Listing and Figures 1A, 1B, 1C, and 2 of the Specification). Variants of SEQ ID NO:1 are described in the Specification at, for example, page 3, lines 10-16; page 11, lines 16-23; page 12, lines 24-27; and page 16, lines 15-17.

One of ordinary skill in the art would recognize polypeptide sequences which are variants having a polypeptide sequence at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polypeptide variants of SEQ ID NO:1. Moreover, the Specification describes antibodies which specifically bind the SEQ ID NO:1 polypeptides. (See the Specification, for example, at page 4, lines 8-10; and pages 23-24.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 10 recites chemical structure to define the claimed genus:

> 10. An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and
>
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base his written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

Embodiments of the present invention are directed, *inter alia*, to antibodies which specifically bind cell junction PDZ related proteins, including cell junction PDZ proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as cell junction PDZ proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites antibodies which specifically bind a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 233 amino acid residues). This variation is far less than that of all potential cell junction PDZ proteins related to SEQ ID NO:1, i.e., those cell junction PDZ proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of September 11, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies that bind specifically to "variants" of SEQ ID NO:1 at the time of filing of this application.

4. Summary

The Examiner failed to base his written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in

the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the polypeptide "variants" recited by the claims, and antibodies which specifically bind those polypeptides. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

VI Obviousness rejections under 35 U.S.C. §103(a)

The Examiner, citing a number of combinations of references (US. Patent Nos.6,051,374 (the '374 patent), 6,210,675 (the '675 Patent), Rousset et al., Alisa Campbell, Bost et al., Harlow et al. and Owens et al.) has rejected claims 10, 30, 31, 33, 35-42 and 45-46 as unpatentable under 35 U.S.C. §103(a) (See 12/03/03 Office Action at pages 9-19). Applicants traverse each and every rejection. Contrary to Examiner's assertions, none of the cited references, alone or in combination, teach or suggest an isolated antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 as is recited in claim 10. Further, none of the cited supporting references correct for this deficiency. Thus contrary to the Examiner's assertions (See 12/03/03 Office Action at page), the skilled artisan would have no reasonable expectation of success in producing the claimed invention.

The rejections are flawed for several reasons. First, none of cite references teach an amino acid sequence of SEQ ID NO:1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1. It may be that the peptides described in the cited references would "bind" a polypeptide comprising SEQ ID NO:1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1. However, the present claims recite an antibody which "**specifically binds**" a polypeptide comprising SEQ ID NO:1 or a naturally occurring amino acid sequence at least 90% identical to

the amino acid sequence of SEQ ID NO:1. In order for an antibody to specifically bind to a polypeptide comprising the amino acid sequence of SEQ ID NO:1 or a "90% variant"of SEQ ID NO:1, one must have the sequence information of SEQ ID NO:1. However, as described above, none of the cited references provide such information. Accordingly, on this basis Applicants respectfully request withdrawal of the rejection.

The rejection is also flawed because the Office Action misinterprets the meaning of the term "specific binding" in applying the cited references. The Examiner uses the term to include an antibody that would bind to more than one protein and thus sets forth an interpretation of the claim for an antibody which would bind in a non-specific manner to proteins.(See 12/03/03 Office Action at page 12). This is an erroneous interpretation. The ordinary meaning of "specific" is "pertaining to, characterizing, or distinguishing a species." (See the attached dictionary definition of specific). Thus, an antibody which specifically binds a polypeptide comprising SEQ ID NO:1 will be able to distinguish the SEQ ID NO:1 polypeptide from other polypeptides. Since none of the cited references teach a polypeptide comprising SEQ ID NO:1 or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, they can not and do not teach an antibody that will be able to distinguish the SEQ ID NO:1 polypeptide or a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 from other polypeptides. Accordingly, on this separate and additional basis, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
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